EXHIBIT A

JOURNAL OF CLINICAL ONCOLOGY

Gefitinib in Combination With Gemcitabine and Cisplatin in Advanced Non–Small-Cell Lung Cancer: A Phase III Trial—INTACT 1

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Submitted August 1, 2003; accepted December 2, 2003.

Supported by a grant from AstraZeneca, Wilmington, DE.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

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0732-183X/04/2205-777/$20.00

DOI: 10.1200/JCO.2004.08.001

ABSTRACT

Purpose
The purpose of this study was to determine whether the addition of the epidermal growth factor receptor tyrosine kinase inhibitor gefitinib (Iressa, ZD1839; AstraZeneca, Wilmington, DE) to standard first-line gemcitabine and cisplatin provides clinical benefit over gemcitabine and cisplatin alone in patients with advanced or metastatic non–small-cell lung cancer (NSCLC). Gefitinib has demonstrated encouraging efficacy in advanced NSCLC in phase II trials in pretreated patients, and a phase I trial of gefitinib in combination with gemcitabine and cisplatin showed favorable tolerability.

Patients and Methods
This was a phase III randomized, double-blind, placebo-controlled, multicenter trial in chemotherapy-naive patients with unresectable stage III or IV NSCLC. All patients received up to six cycles of chemotherapy (cisplatin 80 mg/m² on day 1 and gemcitabine 1,250 mg/m² on days 1 and 8 of the 3-week cycle) plus either gefitinib 500 mg/d, gefitinib 250 mg/d, or placebo. Daily gefitinib or placebo was continued until disease progression. End points included overall survival (primary), time to progression, response rates, and safety evaluation.

Results
A total of 1,093 patients were enrolled. There was no difference in efficacy end points between the treatment groups: for the gefitinib 500 mg/d, gefitinib 250 mg/d, and placebo groups, respectively, median survival times were 9.9, 9.9, and 10.9 months (global ordered log-rank [GOLrank] P = .4560), median times to progression were 5.5, 5.8, and 6.0 months (GOLrank; P = .7633), and response rates were 49.7%, 50.3%, and 44.8%. No significant unexpected adverse events were seen.

Conclusion
Gefitinib in combination with gemcitabine and cisplatin in chemotherapy-naive patients with advanced NSCLC did not have improved efficacy over gemcitabine and cisplatin alone. The reasons for this remain obscure and require further preclinical testing.

J Clin Oncol 22:777-784. © 2004 by American Society of Clinical Oncology

INTRODUCTION

Platinum-based combination chemotherapy constitutes standard treatment for patients with advanced or metastatic non–small-cell lung cancer (NSCLC) and a good performance status. Chemotherapy has demonstrated modest but significant improvements in survival rates over best supportive care [1]. However, the prognosis for patients receiving platinum-based chemotherapy as first-line treatment for advanced NSCLC remains poor and side effects are considerable [2]; therefore, novel agents are urgently needed for this disease. One of the most widely used platinum-based combinations is gemcitabine and cisplatin. In two phase III studies of chemotherapy-naive patients with advanced NSCLC, the response rates for patients receiving gemcitabine and cisplatin were 30.4% to 40.6%, median times to
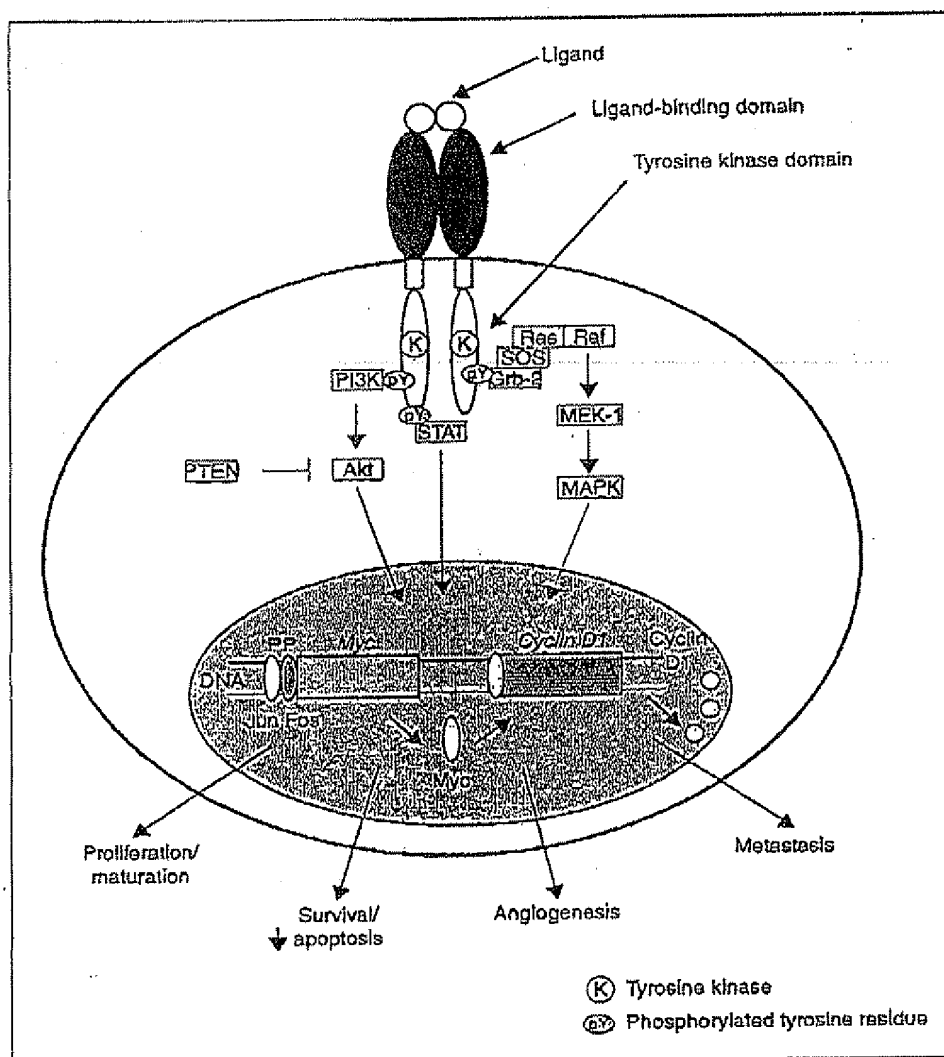
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Fig 1. Epidermal growth factor receptor signal transduction. Adapted with permission [5].

progression were 5.6 to 6.9 months, and overall survival times were 8.7 to 9.1 months [3,4].

The epidermal growth factor receptor (EGFR) has been shown to play an important role in the growth and survival of many solid tumors, including NSCLC. Activation of EGFR enhances the processes responsible for tumor growth and progression, including the promotion of proliferation, angiogenesis, and invasion/metastasis and inhibition of apoptosis (Fig 1) [5-7]. Gefitinib (Iressa, ZD1839; AstraZeneca, Wilmington, DE) is an orally active EGFR tyrosine kinase inhibitor (EGFR-TKI) that blocks the signal transduction pathways implicated in the proliferation and survival of cancer cells [7].

Two phase II trials of gefitinib monotherapy in patients with pretreated advanced NSCLC demonstrated encouraging antitumor activity (objective response rates, 11.8% to

18.4%) and symptom relief (symptom improvement rates, 40.3% to 43.1%) and good tolerability [8-11]. This favorable tolerability profile, coupled with its mechanism of action, which is distinct from that of cytotoxic agents, provides a strong rationale for use of gefitinib in combination with standard cytotoxic regimens. This rationale is supported by data from preclinical studies in which gefitinib potentiated the efficacy of various cytotoxic drugs against a range of human solid tumor types, both in vitro and in vivo [12,13]. In particular, synergy was observed when gefitinib and cisplatin were used in combination, whereas no synergy could be demonstrated between gemcitabine and gefitinib [13].

On the basis of phase I trials of gefitinib monotherapy, two doses were identified for further study based on pharmacokinetics and clinical activity. Gefitinib 250 mg/d is higher than the lowest dose at which clinical responses were

seen (150 mg/d), and 500 mg/d is the highest dose level that is well tolerated for a long period by most patients. A feasibility study of daily oral gefitinib (250 and 500 mg/d) in combination with gemcitabine and cisplatin demonstrated a manageable and predictable tolerability profile with no evidence of any clinically significant pharmacokinetic interactions between gefitinib and cisplatin or gemcitabine [14]. Encouraging antitumor activity was seen in a range of solid tumors at both gefitinib doses in this study [14].

Here we present the results from a multinational, randomized, double-blind, placebo-controlled phase III study. The Iressa NSCLC Trial Assessing Combination Treatment (INTACT) 1 investigated the efficacy and safety of gefitinib (250 and 500 mg once daily) versus placebo in combination with cisplatin plus gemcitabine in chemotherapy-naive patients with advanced NSCLC. The primary objective was to assess whether gefitinib increases overall survival relative to placebo in combination with cisplatin and gemcitabine. A second trial of identical design (INTACT 2) has been conducted to investigate gefitinib in combination with paclitaxel plus carboplatin, another commonly used combination in patients with advanced NSCLC [15].

PATIENTS AND METHODS

Patients were randomly assigned to one of three treatment groups in a double-blind manner. All patients received gemcitabine and cisplatin in combination with gefitinib 500 mg/d, gefitinib 250 mg/d, or placebo. Patients were further stratified by dynamic randomization [16] according to weight loss in previous 6 months ($\leq$ 5% $v >$ 5%), disease stage (III v IV), performance status (0 to 1 v 2), and measurable disease (yes v no).

Treatment

Gefitinib or placebo was administered orally, once daily. Chemotherapy was administered in 3-week cycles for a total of six cycles: intravenous gemcitabine 1,250 mg/m^2 for 30 minutes on days 1 and 8; intravenous cisplatin 80 mg/m^2 after gemcitabine administration on day 1 only. Subsequently, patients continued on gefitinib or placebo until disease progression. One gefitinib/placebo dose reduction (500 to 250 mg/d or 250 to 100 mg/d) was allowed per patient. In the event of grade 3 or 4 adverse events not thought to be due to disease progression or gemcitabine and cisplatin, gefitinib administration could be interrupted for a maximum of 14 days.

Eligibility Criteria

The inclusion criteria included histologically/cytologically confirmed NSCLC, locally advanced stage III disease not curable with surgery or radiotherapy or stage IV disease, aged $\geq$ 18 years, and WHO performance status of 0 to 2. Patients were not eligible for this trial if they had previously received chemotherapy (prior surgery or localized radiation were allowed); were hypersensitive to mannitol, corticosteroids, H$_2$-antagonists, antihistamines or agents formulated with polyoxyethylated castor oil; had received radiotherapy within the last 2 weeks; had unresolved toxicity from previous radiation therapy or incomplete healing from previous surgery; had preexisting motor or sensory neurotoxicity (National Cancer Institute Common Toxicity Criteria $\geq$ grade 2); showed

evidence of severe or uncontrolled systemic disease; had recent conditions requiring medication or uncontrolled significant active infections; had an absolute neutrophil count less than 2,000/mm^3, WBCs less than 4,000/mm^3, or platelets less than 100,000/mm^3; had serum bilirubin greater than 1.25 times the upper limit of reference range (ULRR), ALT or AST greater than 2.5 times ULRR (five times ULRR in the presence of liver metastases), serum creatinine greater than 1.5 times ULRR, or creatinine clearance less than 60 mL/min; were pregnant or breast-feeding; had other coexisting malignancies or malignancies diagnosed within the last 5 years with the exception of basal-cell carcinoma or cervical cancer in situ; or had mixed NSCLC plus small-cell lung cancer. Patients with stable brain metastasis or spinal-cord compression were eligible. All patients signed a written informed consent form, and trial approval was obtained from the ethics committee at each trial center. The study followed the Declaration of Helsinki [17] and good clinical practice guidelines.

Assessments

Overall survival and time to progression were assessed from the date of randomization to the date of patient death and the date of objective disease progression (death was considered a progression event in those patients who died before disease progression), respectively. Patients without documented death or objective progression at the time of the final analysis were censored at the date they were last known to be alive or of their last objective tumor assessment, respectively. Tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors [18]. During the trial and for 30 days after the last dose of gefitinib or placebo, patients were monitored for adverse events, which were graded according to the National Cancer Institute Common Toxicity Criteria. Hematology and biochemistry assessments were performed $\leq$ 7 days before the date of randomization and at each clinic visit.

Statistical Analysis

An Independent Data Monitoring Committee provided ongoing guidance and recommendations for patient management, based on review of the formal interim efficacy analysis, and also reviewed safety data on an ad-hoc basis, as determined by a steering committee. The role of the committee was to provide executive oversight and supervision for the conduct of the trial, through review of trial enrollment, protocol and clinical conduct, and blinded safety data.

Gefitinib was compared with placebo on an intent-to-treat basis with respect to overall survival. The study was designed to have 90% power for a two-sided overall significance level test of the hypothesis that gefitinib increases survival relative to placebo given a hazard ratio of 1.33. Assuming a 1-year survival rate of 30% in the placebo arm, this hazard ratio equates to an increase in median survival of 2.3 months for both gefitinib arms. The final analysis of overall survival was planned to include 750 events. On the basis of the study design assumptions, 1,029 patients were required.

An adaptive survival analysis procedure was used at the final analysis that tested either for a positive or negative gefitinib dose-response relationship based on prospective criteria applied to the observed data. A survival trend test (global ordered log-rank test [GOLrank]) was to be used for a positive dose-response relationship, whereas pairwise log-rank tests would be used for a mixed dose-response relationship [19]. To preserve an overall two-sided 5% significance level, and to account for the use of a GOLrank test

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at an interim analysis, simulations with the adaptive procedure were used to calculate a nominal significance level of 4.4% for the final analysis. According to prospective criteria for the adaptive procedure, the final analysis used a GOLrank test to compare survival between the treatment arms.

A posthoc multivariate analysis with eight prespecified prognostic factors at trial entry (disease stage III v IV; performance status 0 or 1 v 2; weight loss in prior 6 months $\leq$ 5% v > 5%; sex; histology; presence or absence of metastases to bone, liver, or brain) was performed to assess which variables predicted improved survival.

In a posthoc subgroup analysis, stratification and prognostic factors (disease stage III v IV; performance status 0 or 1 v 2; weight loss in prior 6 months $\leq$ 5% v > 5%; presence or absence of metastases to bone, liver, or brain) and subgroups of sex and histology were examined in a univariate model. An unadjusted Cox proportional hazard test was applied to the overall survival data for each subgroup to estimate the hazard ratio and 95% CI for the treatment comparisons of gefitinib 250 or 500 mg/d versus placebo.

RESULTS

Patients

In total, 1,093 patients were enrolled from 155 centers between May 2000 and March 2001. Most patients were enrolled by European trial centers (n = 816; 74.7%), but patients were also enrolled in North America (n = 139; 12.7%), Asia (n = 58; 5.3%), South America (n = 45; 4.1%), and South Africa (n = 17; 1.6%). Almost three quarters of the patients were men and the median age was approximately 60 years. Overall, 998 (90.4%) of the patients were white. Most patients had stage IV disease (n = 757; 69.2%) or IIIB with malignant pleural effusion (n = 239; 21.9%). Most patients (n = 984; 90.0%) had a performance status of 0 or 1. The most common histology types were adenocarcinoma and squamous-cell carcinoma, seen in 504 (46.1%) and 328 patients (30.0%), respectively. The three treatment arms were well balanced (Table 1). The median follow-up duration was 15.9 months.

Efficacy

At each interim analysis, the Independent Data Monitoring Committee recommended that the trial continue. At the time of this analysis, 732 and 628 events were observed for survival and time to progression, respectively, with a minimum follow-up of 12 months for overall survival and 6 months for all other end points. There was no statistically significant difference in overall survival between each of the gefitinib arms and the placebo arm. The median survival times were 9.9 months for each of the gefitinib groups, and 10.9 months for the placebo group (GOLrank P = .4560; Fig 2). One-year survival rates were 43% and 41% for the 500 mg/d and 250 mg/d gefitinib groups, respectively, and 44% for the placebo group. Similarly, median time to progression was 5.5 and 5.8 months for the 500 mg/d and 250 mg/d gefitinib groups, respectively, and 6.0 months in the placebo group, with no statistically significant difference

Table 1. Patient Demographics			
	Gefitinib 500 mg/d (n = 365)	Gefitinib 250 mg/d (n = 365)	Placebo (n = 363)
Sex, %			
Female	27.9	23.3	27.8
Male	72.1	76.7	72.2
Age, years			
Median	61	59	61
Range	31-85	34-83	33-81
Disease stage, %*			
IIIa	3.0	1.6	1.9
IIIb	29.9	25.8	28.4
Without pleural effusion	5.5	6.3	6.6
With pleural effusion	24.4	19.5	21.8
IV	66.8	72.3	68.6
WHO performance status, %*			
0	32.1	34.0	33.9
1	58.1	56.4	55.6
2	9.6	9.6	9.6
Weight loss in previous 6 months, %*			
$\leq$ 5%	62.7	64.1	63.9
> 5%	37.0	35.6	36.0
Disease measurability, %*			
Measurable	94.8	94.8	93.4
Nonmeasurable	4.9	4.9	5.8
Histology, %*			
Squamous	28.8	32.1	29.2
Adenocarcinoma	43.3	48.5	46.6
Squamous and adenocarcinoma	2.7	1.4	1.4
Bronchoalveolar	1.1	0.8	0.3
Undifferentiated	11.6	9.3	11.8
Large cell	11.5	7.7	8.8
Race, %			
White	91.0	90.4	89.8
Black	0.8	1.4	1.4
Asian	1.9	1.6	0.8
Hispanic	1.4	2.6	2.2
Oriental	4.9	3.6	5.8
Other	0.0	0.5	0.0
Metastatic disease, %†			
Lung, other	54.9	53.4	51.0
Bone	30.3	34.8	37.8
Liver	21.7	22.3	20.5
Adrenal tissue	21.3	22.7	19.7
Lymph nodes	10.2	10.2	14.1
Skin or soft tissue	5.7	5.3	7.2
Brain	6.3	4.5	2.8
Other	7.8	4.9	4.8

*Information was not available for all patients.
†Stage IV patients only.

between treatment arms (GOLrank P = .7633; Fig 3). In the posthoc multivariate analysis, a performance status of 2, weight loss, and bone and liver metastases were significant (P < .05) predictors of worse survival outcome. In the posthoc univariate analysis examining known NSCLC prognostic factors and subgroups of sex, time on chemotherapy, and histology, no survival differences were seen
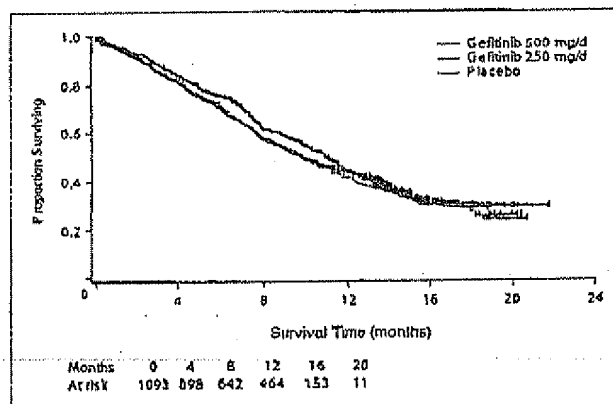
Fig 2. Kaplan-Meier estimates of overall survival in each treatment group. (global ordered log-rank $P = .4560$).

Table 2. Objective Tumor Responses in Each Treatment Group (population assessable for tumor response)

	Objective Tumor Response (%)		
	Gefitinib 500 mg/d (n = 330)	Gefitinib 250 mg/d (n = 336)	Placebo (n = 324)
Complete response	2.1	3.3	0.9
Partial response	48.2	47.9	46.3
Response rate (complete plus partial response)	50.3	51.2	47.2

between treatments for any subgroups of patients [20]. Objective tumor response rates were 50.3% and 51.2% for the 500 mg/d and 250 mg/d gefitinib groups, respectively, and 47.2% in the placebo group ($P = $ not significant). Very few complete responses were seen (Table 2).

Duration of Therapy, Dose Intensity, and Dose Adherence

The dose-intensity of both gemcitabine and cisplatin was similar in all three treatment groups (Table 3), demonstrating that chemotherapy dose intensity was not compromised by the addition of gefitinib. There was a high overall adherence to gefitinib; however, most gefitinib dose interruptions and reductions were seen in the gefitinib 500 mg/d arm (the number was similar in the gefitinib 250 mg/d and placebo arms) [Table 3]. Patients receiving gefitinib 250 mg/d or placebo had a longer therapy duration than those receiving gefitinib 500 mg/d.

Safety and Tolerability

Most adverse events occurred during the combination phase of the trial and many were consistent with the known
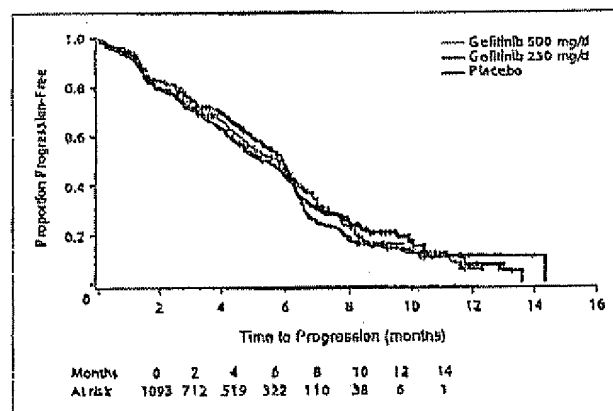

Fig 3. Kaplan-Meier estimates of time to progression in each treatment group. (global ordered log-rank $P = .7633$).

toxicities of the chemotherapy agents. Overall, the safety data from the monotherapy period of the trial support the gefitinib safety profile previously established in phase I and II trials. The most commonly occurring adverse events were gastrointestinal, skin-related, or hematologic in nature. Statistical analysis of prespecified adverse events during the chemotherapy phase revealed no difference between treatment arms except for diarrhea and skin events (diarrhea $P < .0001$ for 500 mg/d v 250 mg/d or placebo; $P = .0924$ for 250 mg/d v placebo; defined skin events $P < .0001$ for all comparisons [no adjustments were made to the P values to take account of the multiple comparisons]), which are known to be associated with gefitinib treatment. A clear dose-response relationship was observed for these events. Interstitial lung disease (ILD)-type events were experienced by three, one, and three patients in the gefitinib 500 mg/d, gefitinib 250 mg/d, and placebo arms, respectively, giving an overall incidence of less than 1%. The incidence of ILD-type events and other respiratory events that were possibly indicative of ILD is summarized in Table 4. No difference in reports of symptoms possibly related to, or indicative of, ILD (eg, dyspnea, increased cough, pneumonia) was seen between the groups.

The most frequently occurring adverse events considered by the investigators to be related to gefitinib/placebo treatment were rash, diarrhea, and acne, which were generally mild (grade 1 or 2; Table 5). No significant additive toxicity was evident in this placebo-controlled setting. Deaths and withdrawals owing to gefitinib/placebo-related toxicity were low and balanced between the three treatment arms. The proportion of patients withdrawn from treatment because of adverse events of any cause was higher (23.0%) for patients in the 500 mg/d group, compared with 14.5% and 11.3% for 250 mg/d and placebo groups, respectively. The types of events leading to withdrawal were similar across the three groups: diarrhea, nausea, vomiting, and acne-like rash.

DISCUSSION

In this study, gefitinib showed no survival benefit over placebo when combined with gemcitabine and cisplatin in a large population of chemotherapy-naive patients with advanced NSCLC. Furthermore, gefitinib did not improve

Table 3. Duration of Therapy, Dose Adherence, and Dose Intensity (population assessable for safety)

	Gefitinib 500 mg/d (n = 358)	Gefitinib 250 mg/d (n = 362)	Placebo (n = 355)
Gefitinib			
Median duration of gefitinib/placebo therapy, days	97	150	159
Dose interruption, %*	45.8	26.8	17.2
Dose reduction, %*	23.2	8.4	2.8
Median dose adherence, %	91.8	97.7	99.5
Chemotherapy			
Median No. of chemotherapy cycles	4	6	6
Gemcitabine median dose-intensity, %	84.2	84.6	85.9
Cisplatin median dose-intensity, %	92.0	91.9	92.4

*Percentage of patients with at least one dose interruption or reduction.

time to progression or objective tumor response over chemotherapy alone. Similar results were seen in the twin study INTACT 2, in which gefitinib was evaluated in combination with paclitaxel and carboplatin [15]. These results are disappointing and surprising because of the significant antitumor activity of gefitinib when given alone to pretreated patients with advanced NSCLC [9,11] and because additive or synergistic activities of gefitinib and several chemotherapeutic drugs have been seen in preclinical models [12]. However, it should be noted that phase II data were not available when these studies were initiated.

The results of two similar trials investigating the use of another EGFR-TKI, erlotinib, in combination with gemcitabine and cisplatin or paclitaxel and carboplatin, have recently been reported. As in our study, the addition of an EGFR-TKI to first-line chemotherapy in patients with advanced NSCLC did not result in any improvement in overall survival over chemotherapy alone.

No significant adverse events were seen that were not predictable from the safety profiles of gefitinib monotherapy and gemcitabine and cisplatin. Furthermore, the safety profile was similar for all treatment arms, with the exception of dose-related additive diarrhea and skin toxicity. As in the phase II gefitinib monotherapy trials, more dose interruptions and reductions of gefitinib were seen in the 500 mg/d arm. Furthermore, although the chemotherapy dose-intensity was similar across the treatment arms,

Table 4. Pulmonary Adverse Events (population assessable for safety)

	Gefitinib 500 mg/d (n = 358)	Gefitinib 250 mg/d (n = 362)	Placebo (n = 355)
Dyspnea, %	17.9	17.7	23.1
Cough, %	15.4	17.7	18.3
Pneumonia, %	3.9	5.5	4.8
ILD event, n	3	1	3

Abbreviation: ILD, interstitial lung disease.

patients on the 500 mg/d arm received a lower median number of chemotherapy cycles. This may have been due to a higher degree of antagonism occurring in this arm, leading to earlier disease progression. These results confirm, in a placebo-controlled setting, that gefitinib has a favorable safety profile and that 250 mg/d is better tolerated than 500 mg/d. Recently published data suggest that gefitinib might be associated with interstitial pneumonia [21]; however, in our study, the overall incidence of ILD was less than 1%, and no imbalance was identified across the three treatment arms in terms of pneumonitis/ILD-type events. One patient receiving gefitinib 250 mg/d and three patients each in the gefitinib 500 mg/d and placebo groups were reported to have experienced an ILD-type event. Furthermore, there was no difference between arms in reports of symptoms possibly related to, or indicative of, ILD, such as dyspnea, cough, or pneumonia. Interestingly, the frequency of ILD-type events in patients receiving gefitinib seems to be higher in Japanese patients (1.9%) than in the rest of the world (0.34%; data on file, AstraZeneca, Wilmington, DE). As yet, the reason for this is unknown, although it may be related to population or environmental differences, or differences in clinical practice.

The reasons for the disappointing efficacy results are still unclear. It is possible that each of the agents is working against a susceptible subpopulation of tumor cells so that the effect is redundant rather than additive, or that one agent results in the loss of an intermediary molecule that is essential to the function of the other agent, resulting in an antagonistic effect.

Patients included in this study and all other studies with gefitinib were not selected on the basis of presence of the target EGFR. Samples from approximately one third of the patients accrued in the study are being immunohistochemically assessed for expression of the receptor. Of course it is conceivable that if only a small number of patients are sensitive to gefitinib, the diluting effect of the lack of selection might make it impossible to discern small differences. A sharper definition of such susceptible subgroups of patients will certainly help in further develop-

Table 5. Commonly Occurring Gefitinib/Placebo-Related Adverse Events (population assessable for safety)

	Adverse Event (%)					
	Gefitinib 500 mg/d (n = 358)		Gefitinib 250 mg/d (n = 362)		Placebo (n = 355)	
	All	Grade 3/4	All	Grade 3/4	All	Grade 3/4
Rash	56.7	12.6	44.5	3.6	21.4	1.1
Diarrhea	50.8	12.0	28.7	3.6	15.5	2.3
Acne	28.2	5.9	18.2	1.4	5.1	0.3
Nausea	19.0	4.5	17.1	2.5	17.5	2.0
Vomiting	17.0	4.7	13.8	2.8	12.4	2.3
Pruritus	12.6	2.0	7.5	0	7.0	0
Asthenia	10.9	2.2	9.7	1.9	10.1	0.8
Dry skin	9.5	0	7.2	0	3.1	0
Anorexia	7.0	1.7	5.2	0.6	4.8	0.3
Thrombocytopenia	7.0	4.2	7.7	5.8	7.9	6.6
Anemia	5.0	2.5	3.9	1.9	6.2	1.7
Neutropenia	5.0	5.0	5.0	5.8	7.0	4.8
Leukopenia	3.9	2.0	2.0	3.3	4.6	2.6
Conjunctivitis	5.3	0.3	0.3	2.5	2.8	0

ment of this type of agent, for which the expression of the target is unlikely to accurately predict the activity of the therapy. In fact, the level of expression of EGFR was not predictive of the sensitivity to gefitinib in a number of in vitro systems [22], and immunohistochemical analysis of samples from the two phase II trials of gefitinib monotherapy in patients with pretreated advanced NSCLC did not provide any evidence of a correlation between EGFR expression levels and either response or symptom improvement. Indeed, substantial numbers of EGFR-negative patients benefited from gefitinib, whereas some patients with intense EGFR staining did not show any response [23].

It seems that inhibition of EGFR autophosphorylation rather than expression of the receptor might impact on the activity of this agent. Furthermore, the assessment of pathways downstream from the activation cascade of EGFR (PI3K/Akt and Ras/Erk) might give more insight into the possibility of inactivating the receptor cascade.

Because no additive effect was observed by administering gefitinib continuously in combination with chemotherapy, possible alternatives could be the administration of gefitinib in the interval between chemotherapy cycles or as maintenance treatment after chemotherapy. This could also potentially prevent the problem of drug interference or antagonism.

In conclusion, INTACT 1 did not show superior efficacy of gefitinib added to gemcitabine and cisplatin in patients with advanced NSCLC. Previous studies have shown

that gefitinib is an active agent for a number of patients with advanced NSCLC, so further work is needed to identify subsets of patients who may benefit more from this therapy. Additional preclinical studies may shed light on the lack of additive or synergistic activity in unselected human tumors.

Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Acted as a consultant within the last 2 years: Giuseppe Giaccone, AstraZeneca; Roy S. Herbst, AstraZeneca; Christian Manegold, AstraZeneca; Giorgio Scagliotti, AstraZeneca; Joan Schiller, AstraZeneca; Ronald Natale, AstraZeneca; Vincent Miller, AstraZeneca; Ulrich Gatzemeier, AstraZeneca; David H. Johnson, AstraZeneca. Received more than $2,000 per year from a company for either of the last 2 years: Ronald Natale, AstraZeneca; Vincent Miller, AstraZeneca.

Appendix

The appendix is included in the full-text version of this article, available on-line at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

REFERENCES

1. Non-small Cell Lung Cancer Collaborative Group: Chemotherapy in non-small cell lung cancer: A meta-analysis using updated data on individual patients from 52 randomised clinical trials. BMJ 311:899-909, 1995

2. Schiller JH, Harrington D, Belani CP, et al: Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 346:92-98, 2002

3. Cardenal F, Lopez-Cabrerizo MP, Anton A, et al: Randomized phase III study of gemcitabine-cisplatin versus etoposide-cisplatin in the treatment of locally advanced or metastatic non-

small-cell lung cancer. J Clin Oncol 17:12-18, 1999

4. Sandler AB, Nemunaitis J, Denham C, et al: Phase III trial of gemcitabine plus cisplatin versus cisplatin alone in patients with locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 18:122-130, 2000

5. Baselga J: New technologies in epidermal growth factor receptor-targeted cancer therapy. Signal 1:12-21, 2000

6. Wells A: The epidermal growth factor receptor (EGFR): A new target in cancer therapy. Signal 1:4-11, 2000

7. Woodburn JR: The epidermal growth factor receptor and its inhibition in cancer therapy. Pharmacol Ther 82:241-250, 1999

8. Douillard J-Y, Giaccone G, Horai T, et al: Improvement in disease-related symptoms and quality of life in patients with advanced non-small-cell lung cancer (NSCLC) treated with ZD1839 ('Iressa') (IDEAL 1). Proc Am Soc Clin Oncol 21:298a, 2002 (abstr 1195)

9. Kris MG, Natale RB, Herbst RS, et al: Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: A randomized trial. JAMA 290:2149-2158, 2003

10. Natale RB, Skarin A, Maddox A-M, et al: Improvement in symptoms and quality of life for advanced non-small-cell lung cancer patients receiving ZD1839 ('Iressa') in IDEAL 2. Proc Am Soc Clin Oncol 21:292a, 2002 (abstr 1167)

11. Fukuoka M, Yano S, Giaccone G, et al: Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer. J Clin Oncol 21:2237-2246, 2003

12. Ciardiello F, Caputo R, Bianco R, et al: Antitumor effect and potentiation of cytotoxic drugs activity in human cancer cells by ZD1839 (Iressa), an epidermal growth factor receptor-selective tyrosine kinase inhibitor. Clin Cancer Res 6:2053-2063, 2000

13. Sirotnak FM, Zakowski MF, Miller VA, et al: Efficacy of cytotoxic agents against human tumor xenografts is markedly enhanced by coadministration of ZD1839 (Iressa), an inhibitor of EGFR tyrosine kinase. Clin Cancer Res 6:4885-4892, 2000

14. Gonzalez-Larriba JL, Giaccone G, van Oosterom A, et al: ZD1839 ('Iressa') in combination with gemcitabine and cisplatin in chemonaive patients with advanced solid tumours: Final results of a phase I trial. Proc Am Soc Clin Oncol 21:95a, 2002 (abstr 376)

15. Herbst RS, Giaccone G, Schiller JH, et al: Gefitinib in combination with paclitaxel and carboplatin in chemotherapy-naive patients with advanced non-small-cell lung cancer: Results from a phase III clinical trial—INTACT 2. J Clin Oncol 22:785-794, 2004

16. Pocock SJ, Simon R: Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 31:103-115, 1975

17. World Medical Association Declaration of Helsinki: Recommendations guiding physicians in biomedical research involving human subjects. JAMA 277:925-926, 1997

18. Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 92:205-216, 2000

19. Rom DM, Costello RJ, Connell LT: On closed test procedures for dose-response analysis. Stat Med 13:1583-1596, 1994

20. Herbst R, Giaccone G, Schiller J, et al: Subset analyses of INTACT results for gefitinib ('Iressa', ZD1839) when combined with platinum-based chemotherapy for advanced non-small-cell lung cancer. Proc Am Soc Clin Oncol 22:627, 2003 (abstr 2523)

21. Inoue A, Saijo Y, Maemondo M, et al: Severe acute interstitial pneumonia and gefitinib. Lancet 361:137-139, 2003

22. Arteaga CL: Epidermal growth factor receptor dependence in human tumors: More than just expression? Oncologist 7:31-39, 2002 (suppl 4)

23. Bailey LR, Kris M, Wolf M, et al: Tumor EGFR membrane staining is not clinically relevant for predicting response in patients receiving gefitinib ('Iressa', ZD1839) monotherapy for pretreated advanced non-small-cell lung cancer: IDEAL 1 and 2. Proc Am Assoc Cancer Res 44:1362, 2003 (abstr LB-170)